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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/562,441	12/28/2005	Siegfried Burggraf	24175-US	3662

22829 7590 12/19/2008
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EXAMINER	
THOMAS, DAVID C	

ART UNIT	PAPER NUMBER
1637	

MAIL DATE	DELIVERY MODE
12/19/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/562,441	BURGGRAF, SIEGFRIED	
	Examiner	Art Unit	
	DAVID C. THOMAS	1637	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *18 July 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *26-32, 34-36, 39 and 45-48* is/are pending in the application.

4a) Of the above claim(s) *45-47* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *26-32,34-36,39 and 48* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

1. Applicant's amendment filed July 18, 2008 is acknowledged. Claim 34 (currently amended) and 26-32, 35, 36, 39 and 48 (previously presented) will be examined on the merits. Claims 45-47 were previously withdrawn and claims 1-25, 33, 37, 38 and 40-44 were previously canceled.

Claim Rejections - 35 USC § 103

2. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

3. Claims 26-32, 34-36, 39 and 48 are rejected under 35 U.S.C. 103(a) as being unpatentable over Wittwer et al. (U.S. Patent No. 6,174,670) in view of Zimmermann et al. (U.S. Patent Pub. No. 2002/0102548).

With regard to claim 48, Wittwer teaches a method for qualitative or quantitative detection of a nucleic acid in a sample (for overview, see Abstract and column 4, lines 32-50), said method comprising the steps of:

adding a control nucleic acid to said sample (internal control nucleic acids are added to PCR reactions for simultaneous amplification and detection, column 41, lines 21-28),

amplifying a test nucleic acid in a sample in the presence of at least one single-stranded detection probe that reversibly binds to a binding region of said test nucleic acid and enables detection of said test nucleic acid (target DNA is amplified using pair of primers in presence of two probes which hybridize to adjacent regions of target during annealing phase of PCR at each cycle, column 3, 58-61, column 7, lines 56-67 and Figure 18, top example; see Figure 2 for probe annealing during phase of lowered temperature);

co-amplifying said control nucleic acid together with said test nucleic acid (internal control nucleic acids are amplified simultaneously with the sample DNA, column 41, lines 28-30),

wherein said control nucleic acid has a binding region that also binds said detection probe and has a nucleotide sequence having at least one deviation in comparison to said binding region of said test nucleic acid (two nucleic acid targets having difference at selected locus are present in reaction which have binding sites for two probes which hybridize at adjacent sites in target wherein one of the probes spans the locus site and is matched with one of the targets and therefore deviates from the sequence of control target, column 7, lines 53-54 and line 64 to column 8, line 9; see Figure 18 for dual probe annealing; genomic DNA that is provided as the control DNA is denatured during the initial amplification step, and therefore is in single-stranded form, while the nucleic acid of some pathogens such as HIV used for the testing of viral load in patients infected with HIV for purposes of prognosis and therapy is inherently single-stranded, column 11, lines 54-60), and

wherein said test nucleic acid and said control nucleic acid form hybrids with said detection probe having melting points sufficiently different to analytically differentiate said hybrids (temperature melting profiles for each target sample are generated that are distinguishable if a true sequence deviation exists between the targets, column 7, line 64 to column 8, line 9 and column 8, lines 25-35; see also Example 23, column 46, lines 20-48, for detection of heterozygous and homozygous forms of methylenetetrahydrafolate reductase (MTHFR) gene and Figure 48), wherein said detection is carried out at a temperature that is 2°C to 10°C below the melting point of said detection probe (monitoring of fluorescence begins at 50°C during melting profile measurements, more than 2°C but less than 10°C below melting temperature of homozygous mutant control for MTHFR gene example, column 46, lines 42-46 and Figure 48).

With regard to claim 26 and 27, Wittwer teaches a method for qualitative or quantitative detection of a nucleic acid in a sample wherein said melting point of said control nucleic acid product is lower than said melting point of said hybrid of said test nucleic acid by at least 5°C (for analysis of point mutation in MTHFR gene, melting point of homozygous mutant is lower than that of wild-type by about 5°C, column 46, lines 20-48 and Figure 48).

With regard to claim 28, Wittwer teaches a method for qualitative or quantitative detection of a nucleic acid in a sample wherein said control nucleic acid and said test nucleic acid are amplified with identical primers (amplification of both control and target nucleic acids are performed with same primers, column 46, lines 27-34).

With regard to claim 29, Wittwer teaches a method for qualitative or quantitative detection of a nucleic acid in a sample wherein said test nucleic acid and said control nucleic acid are amplified by polymerase chain reaction (amplification of control and target nucleic acids is achieved by PCR, column 8, lines 10-18 and column 46, lines 34-46).

With regard to claim 30, Wittwer teaches a method for qualitative or quantitative detection of a nucleic acid in a sample wherein two or more of said test nucleic acids and two or more of said control nucleic acids are present in the same sample (the discriminatory power of hybridization probes can be applied to multiplex PCR using multiple detection probes that sequentially melt off different targets at different temperatures, column 46, lines 49-61; multiplex reactions can be performed with internal control nucleic acids, column 41, lines 21-30).

With regard to claim 31, Wittwer teaches a method for qualitative or quantitative detection of a nucleic acid in a sample wherein said test nucleic acid is derived from a pathogen (nucleic acid from pathogens such as hepatitis B and C, and HIV can be detected using hybridization probes that distinguish wild-type and variants by melting curve profiles, column 35, lines 30-60 and column 41, lines 54-60).

With regard to claim 32, Wittwer teaches a method for qualitative or quantitative detection of a nucleic acid in a sample wherein said detection is carried out in real-time (monitoring of factor V Leiden mutation can be monitored both in real time during each cycle, as well as by performing melting profile after completion of amplification, column 44, line to column 45, line 14 and Figures 46 and 47).

With regard to claim 34, Wittwer teaches a method for qualitative or quantitative detection of a nucleic acid in a sample wherein said melting point of said second products is so low that said hybrid is negligible or not at all present in said detection (melting point of homozygous mutant is comparatively low for factor V Leiden mutation and product appears not be present when monitoring sample at 63°C where both heterozygous and homozygous wild-type are not fully melted, column 44, line 65 to column 45, line 14 and Figure 47).

With regard to claim 35, Wittwer teaches a method for qualitative or quantitative detection of a nucleic acid in a sample wherein only one of said detection probes is used and said detection is based on a melting curve of said test nucleic acid, wherein the melting curve of said control nucleic acid serves as an internal control of proper amplification (example of melting profile for monitoring MTHFR gene mutation is performed using one labeled probe along with a labeled primer, wherein control nucleic acid is amplified and monitored by performing melting curve, which is indicative of proper amplification, column 46, lines 20-48 and Figure 48).

With regard to claim 36, Wittwer teaches a method for qualitative or quantitative detection of a nucleic acid in a sample wherein two of said detection probes are used, said probes forming a FRET pair (two labeled hybridization probes can be used wherein the probes hybridize at closely spaced sites on the target, with one probe being 3'-labeled with fluorescein to allow transfer of energy to nearby Cy5 reporter group on 5' end of second probe, column 31, line 43 to column 32, line 7 and Figure 18).

With regard to claim 39, Wittwer teaches a method for qualitative or quantitative detection of a nucleic acid in a sample wherein said deviation in nucleotide sequence is an exchange of a A or a T for a G or C (factor V Leiden mutation involves G to A mutation, column 42, lines 62-64, while the MTHFR gene mutation involves C to T mutation, column 46, lines 20-26 and therefore there is an exchange of A for G for factor V Leiden and T for C for the MTHFR gene mutation when using wild type genomic DNA as a control compared to the binding region of the test DNA, column 14, lines 35-43).

Wittwer does not teach a method for qualitative or quantitative detection of a nucleic acid in a sample comprising the step of adding a single-stranded control nucleic acid to the sample, wherein the control nucleic acid contains only sequences necessary for amplification and binding of a detection probe and no more than about 10% of additional sequences.

Zimmermann teaches a method of amplification of nucleic acids using a synthetically-produced single-stranded construct that serves as an internal control for the amplification assay (paragraph 2, lines 1-9). The control nucleic acids are as short as 90 bases and contain the forward and reverse primer binding sites flanking short internal random sequences (paragraph 14, lines 1-7 and paragraph 29, lines 1-11). The internal control nucleic acids are added to the sample prior to any pre-purification or extraction steps (paragraph 18, lines 1-10).

It would have been prima facie obvious to one of ordinary skill in the art at the time the invention was made to combine the methods of Wittwer for monitoring and detecting nucleic acid hybridization of probes to target and control molecules using melting curve analysis and those of Zimmermann who teaches methods of nucleic acid amplification using short single-stranded nucleic acid controls that are added to target samples prior to sample processing since the single-stranded nucleic acid controls and methods taught by Zimmermann can be easily adapted for the quantitative methods of Wittwer for measurement of relative copy numbers required for quantifying viral loads in patients infected with RNA-based agents such as HIV or hepatitis C that require single-stranded nucleic acid controls (Wittwer, column 41, lines 52-56) but can also be used for detection of DNA targets (Zimmermann, paragraph 21, lines 7-11). Thus, an ordinary practitioner would have been motivated to use the melting profile methods of Wittwer to analyze the amplification products of target and control nucleic acids that contain binding regions for detection probes that deviate by one or more nucleotides to allow melting point analysis to differentiate the amplification products during quantification since Zimmermann shows that internal control nucleic acids can be readily synthesized and successfully amplified by PCR in single-stranded form for detection of a wide variety of both RNA and DNA targets (Zimmermann, paragraph 20, lines 1-10). These constructs contain random sequences between the flanking primer binding sites (Zimmermann, paragraph 29, lines 1-11) that can easily be modified to bind the real-time detection probes of Wittwer.

Furthermore, single-stranded internal control nucleic acids offer several advantages over controls produced from vectors or obtained from genomic DNA. Amplification assays using single-stranded internal controls can be performed quickly and inexpensively without sacrificing specificity or sensitivity (Zimmermann, paragraph 10, lines 1-4). Moreover, the synthetic nucleic acid controls can be produced automatically in a synthesizer, and eliminates the need for expensive purification in the case of controls made by recombinant DNA techniques Zimmermann, paragraph 12, lines 1-15), thus making them suited for large-scale industrial use (Zimmermann, paragraph 13, lines 1-7), and problems with nonspecific amplification products have not been observed using the short control constructs (Zimmermann, paragraph 14, lines 1-7). Like Wittwer, Zimmermann realizes that it is highly useful to amplify internal controls with the same primers used for the target nucleic acid, paragraph 16, lines 1-5) and is also aware of the practical need and use for controls that are similar in sequence yet vary from the target nucleic acid in distinguishable ways, such as sequence variations (Zimmermann, paragraph 16, lines 6-21).

Finally, Wittwer is keenly aware of the need and advantages of using internal controls for PCR. With regard to multiplex amplification, Wittwer states "Such control amplifications are best done as internal controls with simultaneous amplification and detection" (column 41, lines 28-30). With regard to viral load measurements, Wittwer states "Using a control template and monitoring the efficiency of amplification of both control and natural templates during amplification, accurate quantification of initial copy number is achieved", column 41, lines 56-60). Further in regard to mRNA quantitation

using melting point analysis, Wittwer states "Relative quantification of two PCR products is important in many quantitative PCR applications. Multiplex amplification of two or more products followed by intergration of the areas under melting peaks will be extremely useful in these areas. mRNA is often quantified relative to the amount of mRNA of a housekeeping gene" (Wittwer, column 42, lines 20-25).

Response to Arguments

4. Applicant's arguments filed July 18, 2008 have been fully considered but they are not persuasive.

Applicant argues that the rejection of claims 26-32, 34-36, 39 and 48 under 35 U.S.C. § 103(a) as being obvious Wittwer et al. (U.S. Patent No. 6,174,670) in view of Zimmerman et al. (U.S. Patent Pub. No. 2002/0102548) should be withdrawn since the references do not teach all the limitations of the claims. In the previous office action, the Examiner stated that Wittwer does not teach the limitation requiring that the control nucleic acid be single stranded and consist "essentially of the sequences necessary for amplification and for binding of said probe and no more than about 10% of additional nucleotides". Applicant argues that while the secondary reference of Zimmerman teaches the use of single-stranded constructs as short as 90 nucleotides that serve as internal controls, the combination of the methods of Wittwer and Zimmerman falls short of the present invention since the internal controls of Zimmerman contain considerably more nucleotides than are necessary for primer and probe binding during amplification/detection and would require modification to be useful in the methods of

Wittwer in which the internal controls also contain probe binding sites. Applicant argues that the current invention dispenses with extra nucleotides in the control nucleic acids while the prior art stresses the importance of maintaining the control and target sequences as similar as possible.

The Examiner asserts that both Wittwer and Zimmerman teach the use of internal control sequences that are co-amplified with target sequences using common primers (Wittwer, column 41, lines 28-30 and Zimmerman, paragraph 16, lines 1-3). Zimmerman additionally teaches that the internal controls are short chemically synthesized single-stranded nucleic acids (Zimmerman, paragraph 13, lines 1-7) and the fact that such artificial constructs are made without recombinant techniques reduces the cost and time of preparation of the controls without sacrificing specificity or sensitivity (Zimmerman, paragraph 9 and 10). While Zimmerman teaches amplification and detection using internal control sequences without specific discussion of the use of probes, the reference does indicate that PCR includes TaqMan PCR (Zimmerman, paragraph 6, lines 12-16), which would be recognized by the ordinary practitioner as a method using labeled detection probes. Thus, while control constructs that are at least 90 nucleotides in length would contain primer binding sites of about 20 bases each (SEQ ID NOS 1 and 2, see Table 1), for real-time PCR applications it would be obvious to replace the random internal sequences with a probe binding site, resulting in a control construct with at least 75% essential nucleotides assuming the probe is at least 30 nucleotides in length. Wittwer teaches an amplification/detection system in which primers are preferably no longer than 30 nucleotides and that probes are no longer than

40 nucleotides, though this limitation is not based on function, but rather on cost (Wittwer, column 44, lines 3-27). Thus, the use of short single-stranded internal controls as taught by Zimmerman in the PCR monitoring system of Wittwer using labeled probes would result in probes that contain nearly 100% essential binding nucleotides in control constructs of about 90-100 nucleotides.

Furthermore, it is not clearly defined in the specification or the claims what size range is intended by the phrase "about 10% additional nucleotides". The specification on p. 7 discusses additional nucleotides of up to approximately 30 that may be present in a construct, but the total length is not given, and therefore the percentage of the extra bases cannot be determined. In addition, the example for the internal control on p. 13 includes 21 additional bases out of a total of 120 nucleotides in the internal control sequence, which is about 17%. Thus, the internal controls derived by the combination of the teachings of Wittwer and Zimmerman are "about" the same with respect to amount of additional, or non-essential nucleotides as those of the current invention.

In conclusion, based on all of the arguments discussed above, the 103(a) rejection of claims 26-32, 34-36, 39 and 48 over Wittwer in view of Zimmerman is maintained.

Summary

5. Claims 26-32, 34-36, 39 and 48 are rejected. No claims are allowable.

Conclusion

6. **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Correspondence

7. Any inquiry concerning this communication or earlier communications from the examiner should be directed to David C. Thomas whose telephone number is 571-272-3320 and whose fax number is 571-273-3320. The examiner can normally be reached on 5 days, 9-5:30.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Gary Benzion can be reached on 571-272-0782. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

/David C Thomas/
Examiner, Art Unit 1637

/Kenneth R Horlick/
Primary Examiner, Art Unit 1637